Peyronie's Disease: A Review

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Peyronie's disease is an acquired benign condition without known systemic sequelae with presenting symptoms that include the presence of a plaque or induration of the penile shaft, penile curvature or deformity during erection, penile pain, and erectile dysfunction. This article reviews the natural history of the disease, discusses the disease's etiology (widely thought to involve minor penile trauma with subsequent aberrant wound healing), and outlines proper clinical evaluation of Peyronie's disease patients. Medical treatments can be systemic (colchicine, potassium aminobenzoate, vitamin E), intralesional (steroids, verapamil, collagenase, interferons), or topical. Surgical therapy for Peyronie's disease (plication, graft-based, and prosthetic techniques) should be reserved for the man who has failed conservative therapy and whose curvature, indentation, or erectile dysfunction precludes intercourse. Regardless of the surgical procedure, the patient should be made aware of the inherent risks of surgery.

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Peyronie's disease, first described in 1743,[1] is an acquired benign condition without known systemic sequelae that usually presents with a palpable induration or plaque and curvature or indentation of the erect penis. Occasionally, erectile dysfunction (ED) may be associated with Peyronie's disease, and at times the erections may be painful. During the past decade, significant advances have been made in understanding the pathophysiology of the disease, testing novel medical treatments of Peyronie's disease, and improving the surgeon's ability to successfully reconstruct the "deformed" penis. The current era of phosphodiesterase therapy for the treatment of ED seems to have increased the number of patients presenting for treatment of Peyronie's disease and has simul-

taneously required that our treatments reliably preserve potency. The disease remains, however, an entity imperfectly understood, without a cure, and with a treatment limited only to those severely disabled men who are willing to accept significant complications.

Clinical Features and Natural History

The presenting symptoms of Peyronie's disease include the presence of a plaque or induration of the penile shaft, penile curvature or deformity during erection, penile pain, and ED. A 35-year retrospective study of men in Rochester County, Minnesota, demonstrated the average age of onset of Peyronie's disease to be 53 years, with a prevalence of 388.6 per 100,000 men (0.4%).[2] A recent questionnaire study of men aged 30 to 80 years in Germany revealed that 3.2% of respondents reported palpable penile plaques.[3] This may underestimate the true incidence of penile plaques, as demonstrated by an autopsy study that found lesions of the tunica albuginea in 22 of 100 men with no known symptomatic disease.[4] Although it has been claimed that Peyronie's disease is becoming more prevalent, this is most likely due to the recognition of a bent penis during tumescence in men with ED who are now being treated with phosphodiesterase therapy.

ED, estimated to be present in 30% of cases, plays an integral role in Peyronie's disease.[5] Four factors that contribute to ED in Peyronie's disease are severe penile deformity preventing intercourse, a flail penis, impaired vascular function, and psychological distress or anxiety due to the appearance of the penis.[6] A flail penis may occur because of extensive circumferential plaque. Lopez and Jarow[7] reported that, in a study of 76 men with Peyronie's disease, 36% had arterial disease and 59% had veno-occlusive disease as causes of ED. Venous leakage is thought to occur when altered compliance prevents the passive transtunical occlusion of venous channels. ED is not only a possible symptom of Peyronie's disease but also remains a complication of any reconstructive surgery; therefore, its presence and degree is one of the most important factors to consider when weighing surgical options.

The natural history of Peyronie's disease was once thought to entail a slow, spontaneous resolution. However, a survey of 97 men with disease of 1- to 5-years duration reported that 14% had resolving symptoms, 40% had progressive disease, and 47% had stable symptoms.[8] Current understanding of the disease divides patients into an active phase and a mature or stable phase. The onset of disease at times is associated with painful erections and a changing configuration of the plaque and curvature of the erect penis. Up to one third of patients, however, may present with a painless curvature. The painful erections typically resolve over 6 months, and the penile deformity stabilizes by 12 months. The stable phase consists of a painless, stable deformity with a mature scar and, in many instances, development or progression of ED. Features associated with the disease that do not resolve spontaneously include signs and symptoms of longer than 2-years duration, Dupuytren's contractures, and calcified plaque.

Most investigators now concur that minor sexual trauma is the major cause of Peyronie's disease.

Etiology

In 1957, Furey[9] initially suggested (and most investigators now concur) that minor sexual trauma is the major cause of Peyronie's disease. A survey of 732 patients demonstrated an association between penile trauma and both Peyronie's disease and ED.[10] Dorsal and ventral sheer stresses, common during sexual activity, could account for the typical dorsal location of plaques.[11,12]

Clinical research suggests that Peyronie's disease represents an aberration of localized wound healing. Fibrin deposition is one of the initial consequences of microvascular injury, and fibrin has been localized in the tunical tissue in most plaques, some years after development of the disease.[13] Perivascular round cell infiltration has been seen in tissue adjacent to diseased tunica in Peyronie's patients.[14] Plaques consist of dense, immature type 3 collagen with reduced and fragmented elastic fibers.

Experimental incision of the tunica in a rat model resulted in the formation of inflammatory changes seen in the acute phase of Peyronie's disease, including increased expression of transforming growth factor (TGF)-β1.[15–18] TGF-β1 has a pleiotropic effect on fibroblast activity, increasing collagen synthesis while inhibiting connective tissue breakdown via decreased collagenase expression. The ability of TGF-β1, a potent profibrotic cytokine, to induce its own production is considered key to the development of excessive scarring and fibrosis.[19]

Minor penile trauma is ubiquitous, however, and cannot fully explain the etiology of Peyronie's disease. Although Peyronie's disease has not been linked to any predisposed pop-

ulations, there are several conditions associated with the disorder: Paget's disease of the bone, Dupuytren's contracture, and certain human leukocyte antigen subtypes. A family history can be elicited in 2% of cases.[20] Peyronie's disease presents in 16% to 20% of men with Dupuytren's contractures, a disease inherited in an autosomal dominant fashion.[21,22]

In addition to a genetic element, an autoimmune component may be present, as evidenced by the finding of abnormal serologic tests in 785 men with Peyronie's disease[23] and the finding of elevated anti-elastin antibodies in the sera of men with the disease.[24] It has been hypothesized that susceptible men respond to mechanical stress or microvascular trauma with a genetically aberrant wound healing process that involves the expression of growth factors and cytokines.

Our current thinking regarding the etiology of Peyronie's disease is that trauma to the tunica allows intravasation of fibrin from the blood into the tunica. It appears as if fibrin is responsible for initiating the release of the profibrotic compound TGF-β1 within the tunica, which induces the formation of reactive oxygen species (ROS), and it is ROS that leads to the pathologic hallmarks of Peyronie's disease (ie, increased collagen deposition, disorganization of the newly deposited collagen, decrease in the breakdown of the newly deposited collagen, and calcification of the plaque).

Clinical Evaluation

A review of the history and symptoms of a patient with Peyronie's disease should include the duration of the disease, the presence or absence (or resolution) of pain, an estimation of the degree of the penile deformity, and the orientation of the bend. The presence of penile shortening, an hourglass-type indentation, and the number and location of plaques will all affect treatment options. Questions regarding family history, presence of associated conditions, infections, and instrumentation are of interest but do not bear upon treatment of the disease. The most important information to obtain is how the disease impacts the lives of the patient and his partner and the patient's expectations of therapy.

Physical examination should include an assessment of the pubis-to-glans length (because most men recognize a shortening of the penis primarily in the erect state, but in many men it is also recognizable in the flaccid state), the number and position of plaques, and the degree of plaque calcification. Photographs of the erect penis, as seen in Figure 1, or use of an intracorporeal injection to elicit an erection that demonstrates the degree and angle of the defect are helpful for following the course of the disease and for surgical planning, if that is to be considered. Occasionally, sonography is useful in identifying the number and site of plaques as well as the presence of calcification, but we have found sonography to be of limited clinical use in our practice.

Treatment

Medical Treatment

Conservative therapy is the standard treatment of Peyronie's disease. Patients with evolving disease should be treated medically until the disease has become stable, typically a period of at least 6 months but more commonly 12 months. A number of treatments have been offered to men over the years, beginning with Peyronie's own use of mercury and mineral water. Unfortunately, there are few prospective, blinded, randomized, placebo-controlled studies with standardized outcomes of sufficient power to evaluate many of the proposed medical therapies. In evaluating medical therapies, as seen in Table 1, it must be remembered that the natural history of Peyronie's disease includes spontaneous resolution of pain, typically within 6 months, and in some men a small improvement in penile curvature. Medical treatments are administered systemically, locally, or intralesionally.

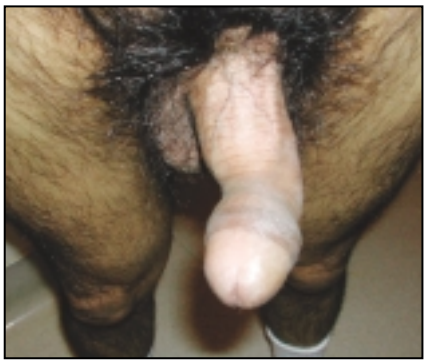

Figure 1. *Penis with Peyronie's disease that demonstrates both a curvature and hourglass deformity during tumescence induced by an intracorporeal injection.*

Colchicine is an oral antimicrotubule agent that inhibits collagen secretion. It is administered at a recommended dose of 0.6 mg to 1.2 mg daily during the first week of treat-

Table 1
Medical Therapy Options for Peyronie's Disease

- Systemic
  - Vitamin E
  - Potaba
  - Colchicine
  - Tamoxifen
  - Acetyl-L-carnitine
- Intralesional
  - Verapamil
  - Collagenase
  - Interferons
- Extracorporeal shock wave therapy

ment, then increasing up to 2.4 mg/d, in divided doses for a period of up to 3 months. The main adverse effect is gastrointestinal upset with diarrhea in up to one third of subjects. Other, more severe side effects include lowered blood counts and elevation of liver enzyme levels. In an uncontrolled study of 24 patients, colchicine was reported to decrease plaque size and improve penile curvature in 50% of patients.[25]

Potassium aminobenzoate (Potaba; Glenwood, Englewood, NJ) has been prescribed extensively for Peyronie's disease.[26] Its mechanism of action is not understood but may involve decreased fibrogenesis through altered serotonin levels. The drug is prescribed at 20 g/d for 3 months, although some practitioners give the drug for up to 12 months. This treatment is expensive and, in general, poorly tolerated. The most frequent reported side effect is gastrointestinal upset. In a review of 2653 patients, Potaba, in a non-controlled study, was reported successful in 57% of treated patients.[27]

Tamoxifen is thought to facilitate the release of TGF-β1 from fibroblasts and therefore to regulate the immune response.[28] In a placebo-controlled study of 25 patients with Peyronies's disease, there was no significant improvement in pain, curvature, or plaque size with tamoxifen, 20 mg twice daily, compared with placebo. Side effects of tamoxifen included gastrointestinal distress and alopecia.[29] Acetyl-L-carnitine, 1 g twice daily, was compared with tamoxifen in a randomized study of 48 patients. With a short follow-up, the patients who received acetyl-L-carnitine had greater decreases in penile pain and plaque size, with fewer adverse effects, compared with those who received tamoxifen.[30]

Vitamin E is commonly used to treat Peyronie's disease. In 1948, Scott and Scardino[31] reported a beneficial effect in 23 men treated with a dosage of 200 mg/d to 300 mg/d. In 1990, a controlled study of vitamin E failed to demonstrate a significant difference in pain, bend, ability to have intercourse, and overall disease state compared with placebo.[8] The proposed action of vitamin E is through its ability to scavenge free radicals like ROS. Many clinicians consider this inexpensive, virtually side effect–free drug a reasonable treatment to offer patients awaiting stabilization of disease, allowing the clinician to build a rapport with the patient.

Several intralesional therapies have been proposed and studied for the treatment of Peyronie's disease. Steroids have been injected into plaque in an effort to exploit their anti-inflammatory properties. Several short-term studies have been reported with good responses; however, intralesional steroids have many local adverse effects, including tissue atrophy and thinning of skin.[32] The use of intralesional steroids may help persistent plaque pain, but they should not be used to treat curvature.

Intralesional injection of the calcium channel blocker verapamil has been reported for the treatment of Peyronie's disease.[33] Calcium channel blockers affect cytokine expression associated with the early phases of wound healing and have been shown to increase the activity of collagenase.[34] Verapamil, 10 mg in 10 mL of saline, is injected every other week for a total of 6 injections, with pain and bruising the most common reported adverse effects. In a recent prospective study of 156 men treated with intralesional verapamil, of those who completed the treatment, 60% had an objective decrease in curvature, 80% an increase in rigidity distal to the plaque, and 71% an increase in sexual function.[35] This study is notable for objectively measuring penile curvature through dynamic penile duplex ultrasound and correlating these findings with subjective patient questionnaire results. Interestingly, those patients who responded to therapy included men with dynamic and stable disease and men with disease ranging from mild to severe.

Gelbard and colleagues[36] reported on the use of intralesional collagenase in a double-blind, placebo-controlled trial, with some benefit over placebo for mild disease but no significant improvement in more severe curvature. Several clinical trials of intralesional interferons have been reported. Interferons inhibit fibroblast proliferation in culture and increase the production of collagenase.[37] Most patients receiving this treatment report transient flu-like symptoms. One study reported favorable results,[38] but this has not been borne out in another published report.[39]

Those patients who responded to verapamil therapy included men with dynamic and stable disease and men with disease ranging from mild to severe.

Several topical therapies have been reported, often employing iontophoresis for drug delivery. Treatment cocktails have included orgotein, steroid, and verapamil.[40] Improvement as measured by history and ultrasound was reported in 62% to 90% of patients, depending on the treatment group, but none of these studies have been controlled.

Local extracorporeal shock wave therapy (ESWT) has been studied. Clearly, this therapy aims to fracture the calcified plaques, but the effect

this has on the pathophysiology of the disease is unclear. Abdel-Salam and colleagues[41] treated 24 patients with between 4 and 10 sessions of ESWT and reported a 59% improvement. A recent study of 42 patients treated with at least 3 sessions of ESWT (3000 shock waves 0.11–0.17 mJ/mm^2) reported subjective improvement in 81% of patients, with 14% claiming excellent results and 50% endorsing significant improvements.[42]

Up to 30% of men with Peyronie's disease have concomitant ED. These patients should be treated no differently than patients with ED who do not have Peyronie's disease. Most such patients are started out on oral phosphodiesterase therapy and, if this fails, intracorporeal injections are then prescribed. The manufacturers of injectable alprostadil specifically state that their product is contraindicated in men with Peyronie's disease, but the reason for this is that up to 30% of men on long-term injectable therapy will develop palpable Peyronie's disease– like nodules of the tunica albuginea. It is theoretically possible that repeat needle puncture could exacerbate Peyronie's disease.

Surgical Therapy

The goal of surgical therapy is simply to make the 2 sides of the penis equal in size. Either lengthening the shorter side or shortening the longer side can accomplish this. When one attempts to lengthen the shorter side, a graft must be interposed and can be composed of autologous tissue, cadaveric tissue, or synthetic material. To shorten the longer side, a plication procedure is used. The ideal candidate for surgical therapy is a man who has failed conservative therapy and whose curvature, indentation, or ED precludes intercourse. When ED is present with Peyronie's disease, one option is a penile implant, which should straighten the penis and elicit an on-demand erection. Regardless of the surgical procedure that is agreed upon by the patient, he should be made aware of all inherent risks, including failure to completely straighten the penis, ED, shortening of the penis, sensory changes in the penis, and occasionally progression of disease.

Tunical shortening procedures are performed on the convex aspect of the penis, opposite the location of greatest deformity.

Plication techniques. Tunical shortening procedures are performed on the convex aspect of the penis, opposite the location of greatest deformity. Nesbit[43] first described the concept by excising an ellipse of tunica albuginea in patients with congenital penile deformities. Pryor and Fitzpatrick[44] first applied the technique to Peyronie's disease in 1979. Typically, the Nesbit ellipse is 1 mm wide for every 10 degrees of deformation. In a study of 359 operations over a 15-year period, 82% of cases were successful, with men regaining their ability to have intercourse.[45] Men who are good candidates for plication-based reconstruction are those patients with good erectile function and adequate penile length, without an hourglass-type narrowing. A study of patient failures identified 3 factors that were associated with poor outcome: impaired erectile function, penile shortening of greater than 2 cm, and penile deformity greater than 30 degrees.[46]

Several modifications of the Nesbit plication have been made, including the Yachia procedure, which relies on the horizontal closure of a longitudinal incision in a Heineke-Mikulicz fashion.[47] This technique can be based on a long incision or several shorter cuts. Successful results of this procedure range from 80% to 95%, and the complications are similar to those of the Nesbit plication. Essed and Schroeder[48] popularized simple plication without incising tunical tissue as a viable treatment of Peyronie's disease. A recent report by Gholami and Lue[49] of 124 patients who underwent simple plication without excision, followed for a mean of 2.6 years, demonstrated a patient-measured outcome satisfaction of 96%. An advantage of the simple plication approach over the traditional Nesbit repair or the Yachia modification is the lack of dissection of the neurovascular bundle and the corpus spongiosum, thus limiting postoperative erectile impairment. It has been estimated that de novo impotence resulting from all variants of plication occurs in approximately 5% of cases.[50]

Graft-based techniques. Plication techniques are limited in their ability to straighten a severely bent penis secondary to the subsequent shortening they cause. Furthermore, certain clinical conditions, such as a circumferential plaque causing an hourglass deformity, cannot be treated by plication. Graft-based reconstruction procedures have therefore been developed to treat these more complicated problems. Devine and Horton[51] first described successful repair of Peyronie's defects using dermal grafts. Long-term follow-up of graft excision techniques has shown low patient satisfaction; one study of 418 men demonstrated that 17% required further surgery for persistent curvature and that 20% of patients had significant erectile impairment.[52] In 1991, Gelbard and Hayden[53] proposed

plaque incision and grafting as a method to decrease the complications associated with plaque excision, namely ED. ED following plaque excision is thought to be due to damage of the underlying erectile tissue, loss of compliance of the new graft, and new venous channels giving rise to veno-occlusive disease. A further complication of graft-based techniques is loss of sensation that occurs as a result of damage to the neurovascular bundle, owing to the increased dissection of Buck's fascia required to expose the tunica albuginea.

The search for an ideal grafting material continues. Autologous tissues employed for grafting have included temporalis fascia, tunica vaginalis, penile skin, and saphenous vein. Cadaveric tissues, such as dermis, fascia, pericardium, and porcine small intestine submucosa, have been employed, as have synthetic materials such as Gore-Tex and Dacron. A report on 113 men treated with saphenous vein grafting and followed for up to 18 months reported satisfactory straightening of the penis in 96%, de novo ED in 12%, and a change in penile sensation lasting longer than 6 months in 10%.[54] Two new materials being used are porcine small intestine submucosa (Surgisis, Cook Urological, Spencer, IN) and human pericardium (Tutoplast, Mentor, Santa Barbara, CA), with satisfactory results being reported in small patient groups followed for 11 to 14 months,[55,56] although our personal data are somewhat disappointing at 12 months with this latter product.

Prosthesis techniques. Penile prostheses in Peyronie's disease are currently reserved for men with ED not responsive to medical therapy. This technique provides excellent results and may be used with modern inflatable prostheses.[57] In most patients with mild curvature, no further procedure is necessary. Wilson and colleagues[58] have reported on the ability to further straighten the penis during prosthesis placement by performing intraoperative modeling without an increase in rate of revision. In cases of severe deformity, plaque incision with or without grafting may be necessary during prosthesis placement, with care taken to avoid damage not only to the implant[59] but also to the neurovascular bundle.

Conclusion

Increasing knowledge of the pathophysiology of Peyronie's disease has fueled clinical and scientific interest in this fibrotic disorder. Current studies examining medical therapies for Peyronies's disease suffer from a lack of prospective, controlled study design, and few reports include objective findings and outcomes. The last decade of surgical therapy can be best described as "less is more," trying to better match those procedures to men who will experience satisfactory outcomes while limiting unacceptable side effects. It is hoped that future therapies may be directed at curing the disease itself rather than limiting its mechanical sequelae. ■

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Main Points

- The presenting symptoms of Peyronie's disease include the presence of a plaque or induration of the penile shaft, penile curvature or deformity during erection, and penile pain; erectile dysfunction (ED) is estimated to be present in 30% of cases.
- A review of the history and symptoms of a patient with Peyronie's disease should include the duration of the disease, the presence or absence (or resolution) of pain, an estimation of the degree of the penile deformity, and the orientation of the bend; the most important information to obtain is how the disease impacts the lives of the patient and his partner and the patient's expectations of therapy.
- Conservative therapy is the standard treatment of Peyronie's disease, and patients with evolving disease should be treated medically until the disease has become stable, typically a period of at least 6 months but more commonly 12 months. Medical treatments are administered systemically, locally, or intralesionally.
- The ideal candidate for surgical therapy is a man who has failed conservative therapy and whose curvature, indentation, or ED precludes intercourse. The goal of surgical therapy is simply to make the 2 sides of the penis equal in size, either by lengthening the shorter side (using a graft) or shortening the longer side (using a plication procedure).
- Penile prostheses in Peyronie's disease are currently reserved for men with ED not responsive to medical therapy. This technique provides excellent results and may be used with modern inflatable prostheses.

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